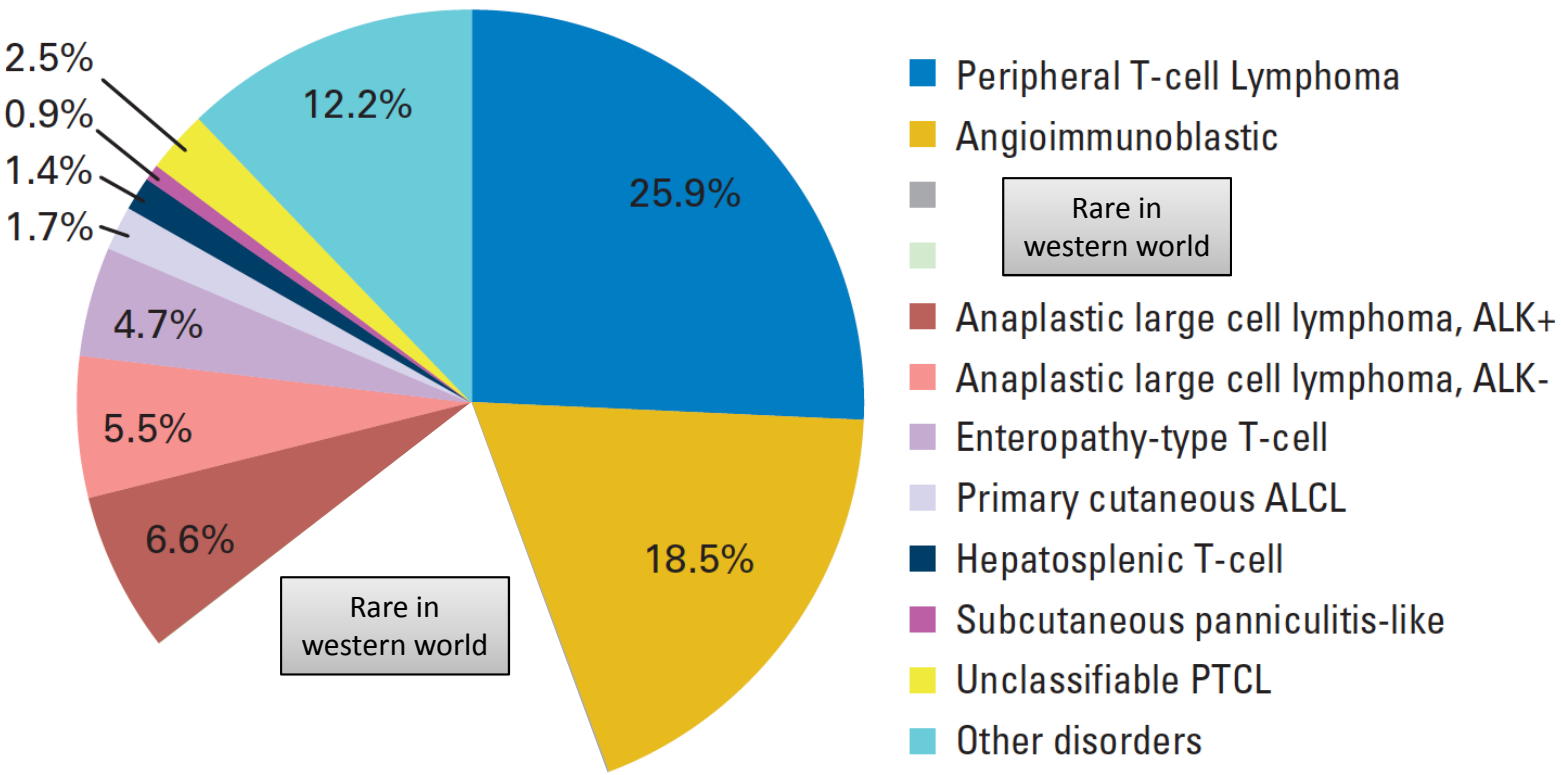
6th International Workshop on PET in Lymphoma
Palais de l'Europe. Menton, France
September 20 -21, 2016

Peripheral T-Cell lymphoma: Old and new prognostic factors.

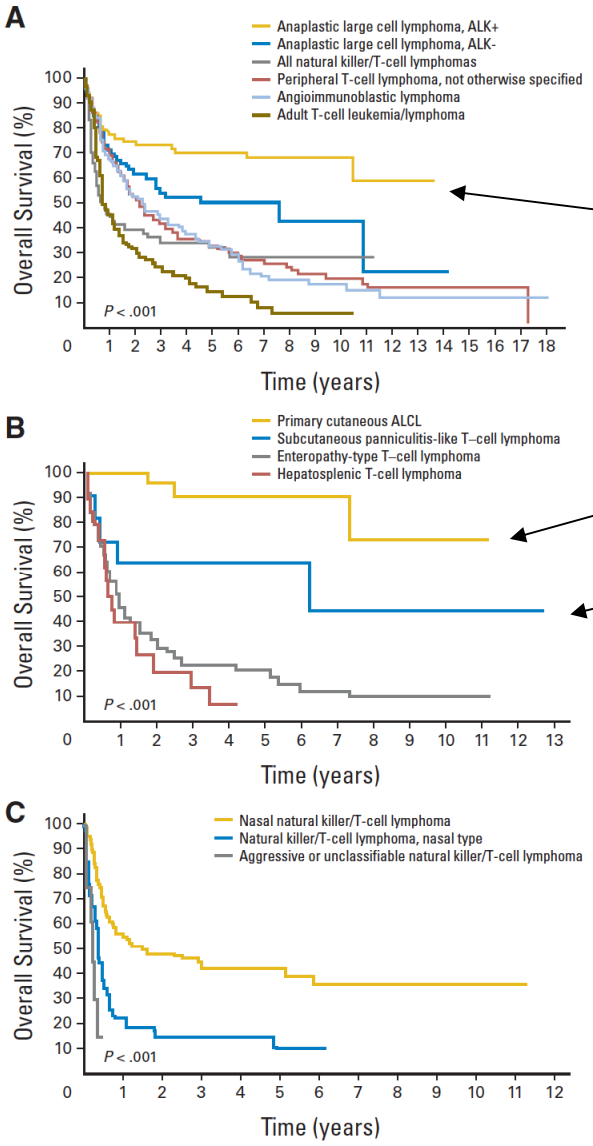
Pr. Andrea Gallamini
Département de recherche et innovation médicale
Hopital A. Lacassagne. Nice (France).

PTCL: subtype frequencies



Int. T- Cell Project Vose JM et al. *J Clin Oncol* 26:4124-4130, 2008

PTCL Prognosis definition:



ALCL Alk +

CTCL

SCPL-TCL

The best prognostic model is a correct diagnosis !

International T-cell project. J Clin Oncol 2008; 26:4124-4130.

Expert Agreement (morphology and IHC) with Consensus Diagnosis

Histotype	Consensus	Histotype	Consensus
ALCL, ALK+	91%	PTCL, unspecified	74%
ATLL	93%	Panniculitis-like	75%
Nasal NK/T-cell	84%	ALCL, ALK-	74%
Angioimmunoblastic	81%	Hepatosplenic	72%
Enteropathy-type	79%	Cutaneous ALCL	66%

Int. T- Cell Project Vose JM et al. *J Clin Oncol* 26:4124-4130, 2008

Plenary Paper

LYMPHOID NEOPLASIA

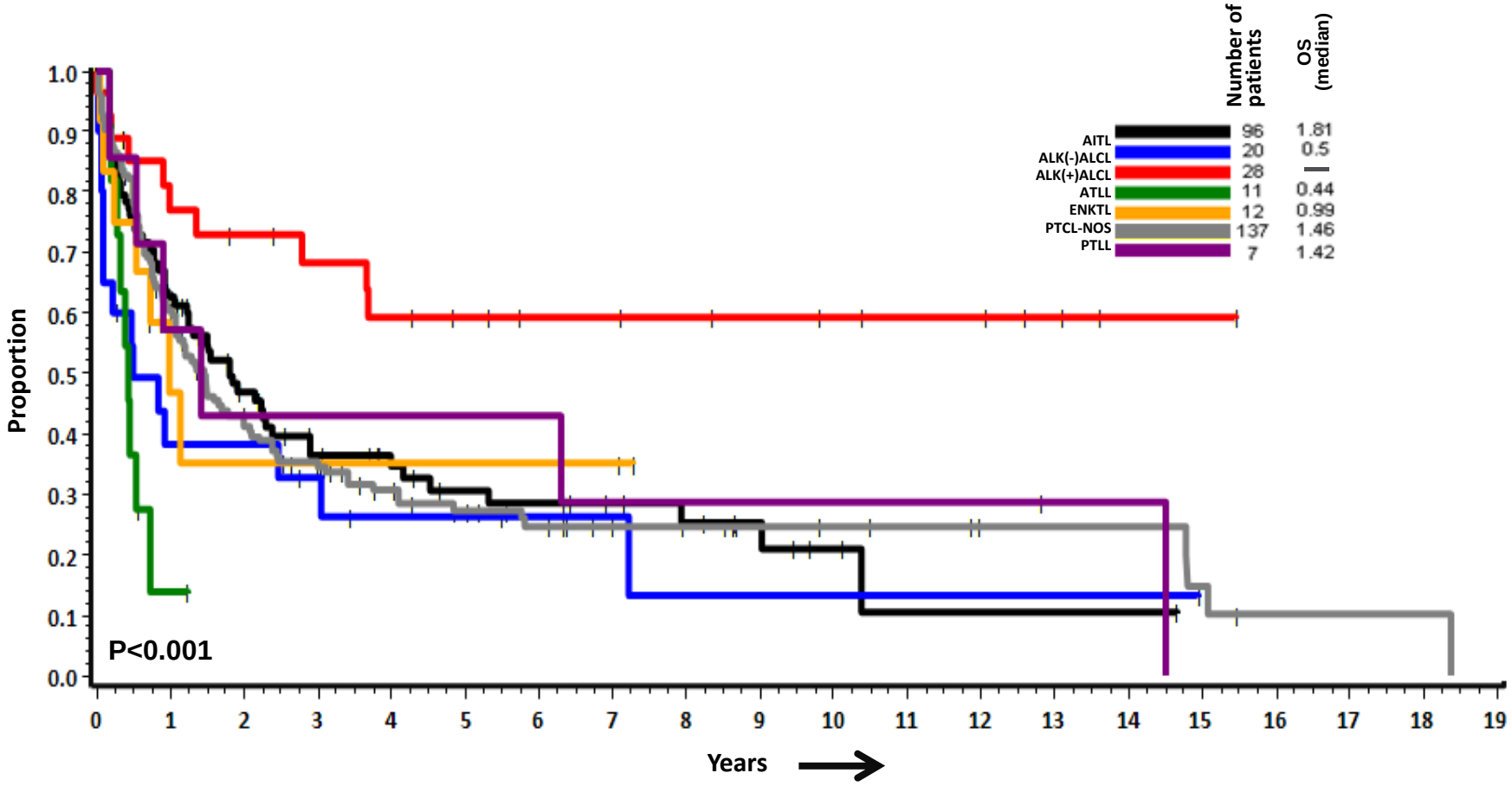
Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma

Javeed Iqbal,[1] George Wright,[2] Chao Wang,[1] Andreas Rosenwald,[3] Randy D. Gascoyne,[4] Dennis D. Weisenburger,[5] Timothy C. Greiner,[1] Lynette Smith,[6] Shuangping Guo,[1] Ryan A. Wilcox,[7] Bin Tean Teh,[8] Soon Thye Lim,[8] Soon Yong Tan,[8] Lisa M. Rimsza,[9] Elaine S. Jaffe,[10] Elias Campo,[11] Antonio Martinez,[11] Jan Delabie,[12] Rita M. Braziel,[13] James R. Cook,[14] Raymond R. Tubbs,[14] German Ott,[15] Eva Geissinger,[3] Philippe Gaulard,[16] Pier Paolo Piccaluga,[17] Stefano A. Pileri,[17] Wing Y. Au,[18] Shigeo Nakamura,[19] Masao Seto,[19] Francoise Berger,[20] Laurence de Leval,[21] Joseph M. Connors,[4] James Armitage,[22] Julie Vose,[22] Wing C. Chan,[6] and Louis M. Staudt,[2] for the Lymphoma Leukemia Molecular Profiling Project and the International Peripheral T-cell Lymphoma Project

The Lymphoma Leukemia Molecular Profiling Project (LLMPP),
(University of Nebraska, Singapore, Bologna, Paris-Creteil, Lausanne)
The International Peripheral T-cell Lymphoma Project (IPTCL)
University of Nebraska (UNMC)
National Cancer Institute/National Institute of Health (NCI/NIH)

Iqbal J: Blood. 2014;123(19):2915-2923

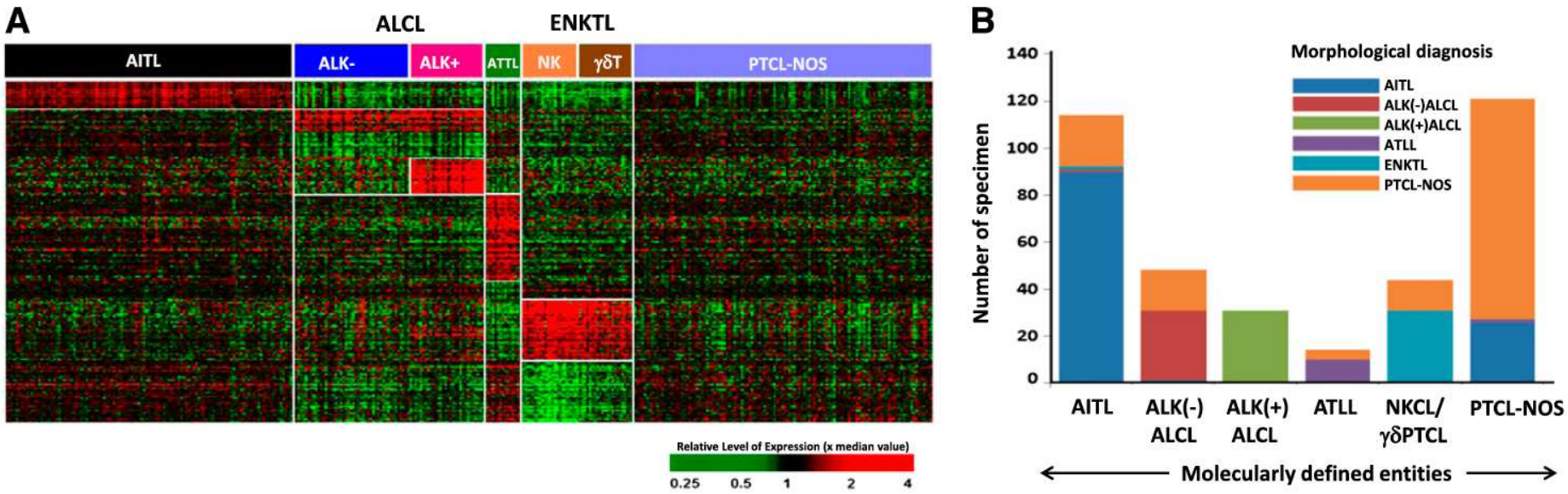
Overall survival by morphological diagnosis (N= 372)



-ALK(+)ALCL patients shows better clinical outcome, whereas ATLL patients show significantly poor overall survival.

Iqbal J: Blood. 2014;123(19):2915-2923

Morphological and molecular diagnosis (N= 372)



-Of 152 PTCL-NOS, 56 cases (37%) were classified into

i. **AITL [14%]**
ii. **ALK(-)ALCL [11%]**
iii. **ATLL [03%]**
iv. **γδ- PTCL [09%]**

- Of 117 AITL, 26 cases (22%) were changed to PTCL-NOS.

Iqbal J: Blood. 2014;123(19):2915-2923

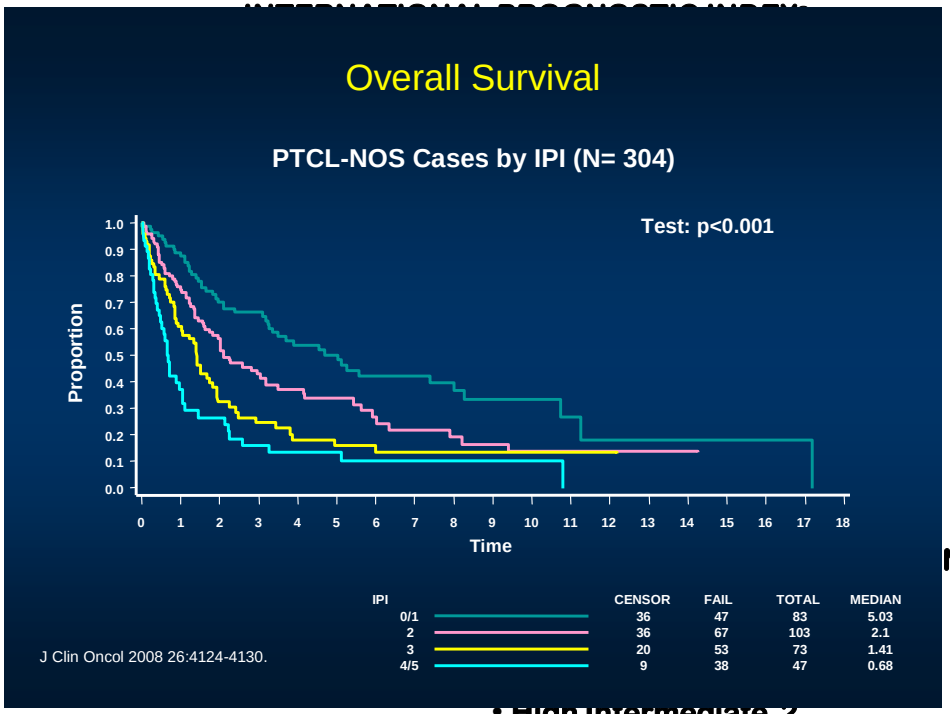
Clinical prognostic models in PTCL

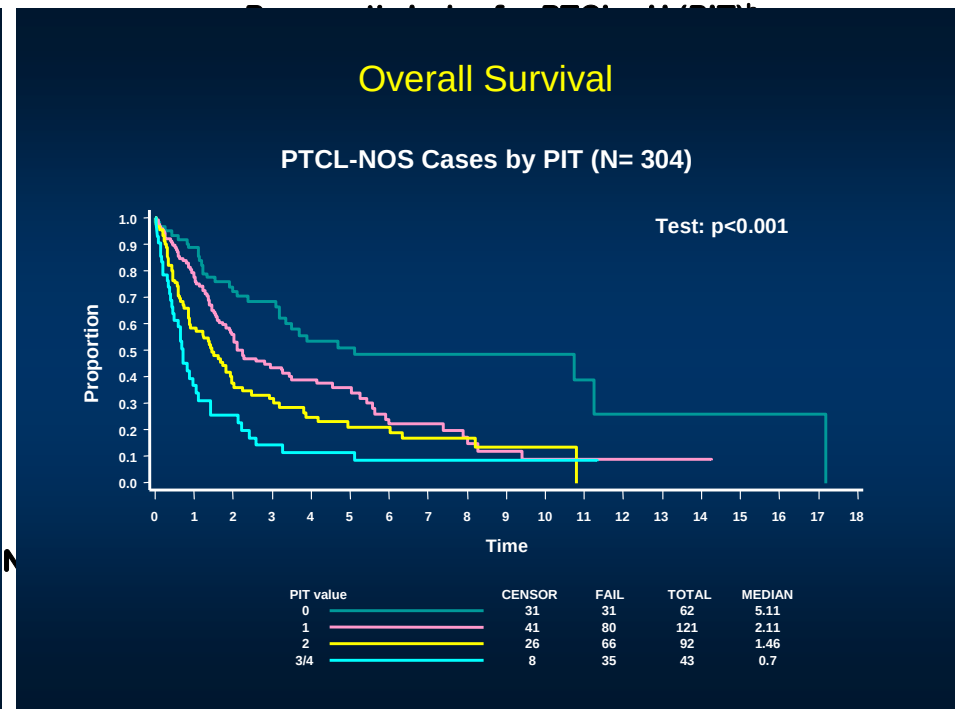
- The number of prognosticators (single or included in models) is inversely related to disease curability
- In PTCL, at least seven different prognostic models have been proposed so far.

IPI (International Prognostic Index):	NHL	Shipp 1993
PIT (Prognostic model for PTCL)	PTCL-U	Gallamini 2004
IPTCLP (International PTCL Project)	PTCL	Vose 2005
mPIT (Modified PIT)	PTCL-U	Went 2006
AIP (Angioimmunoblastic TCL Prognostic Index)	AITL	Tokunaga 2012
KPI Korean Prognostic Index for NK/T cell “nasal-type” lymphoma	NKTCL	Lee 2006
B_2M-Age model for ALCL	ALCL	Sibon 2012

NCCN Guidelines™ Version 3.2016
Peripheral T cell Lymphoma

NCCN Guidelines Index
NHL Table of Contents
Discussion





- **Performance status 2-4**
- **High intermediate 2**
- **High 3**

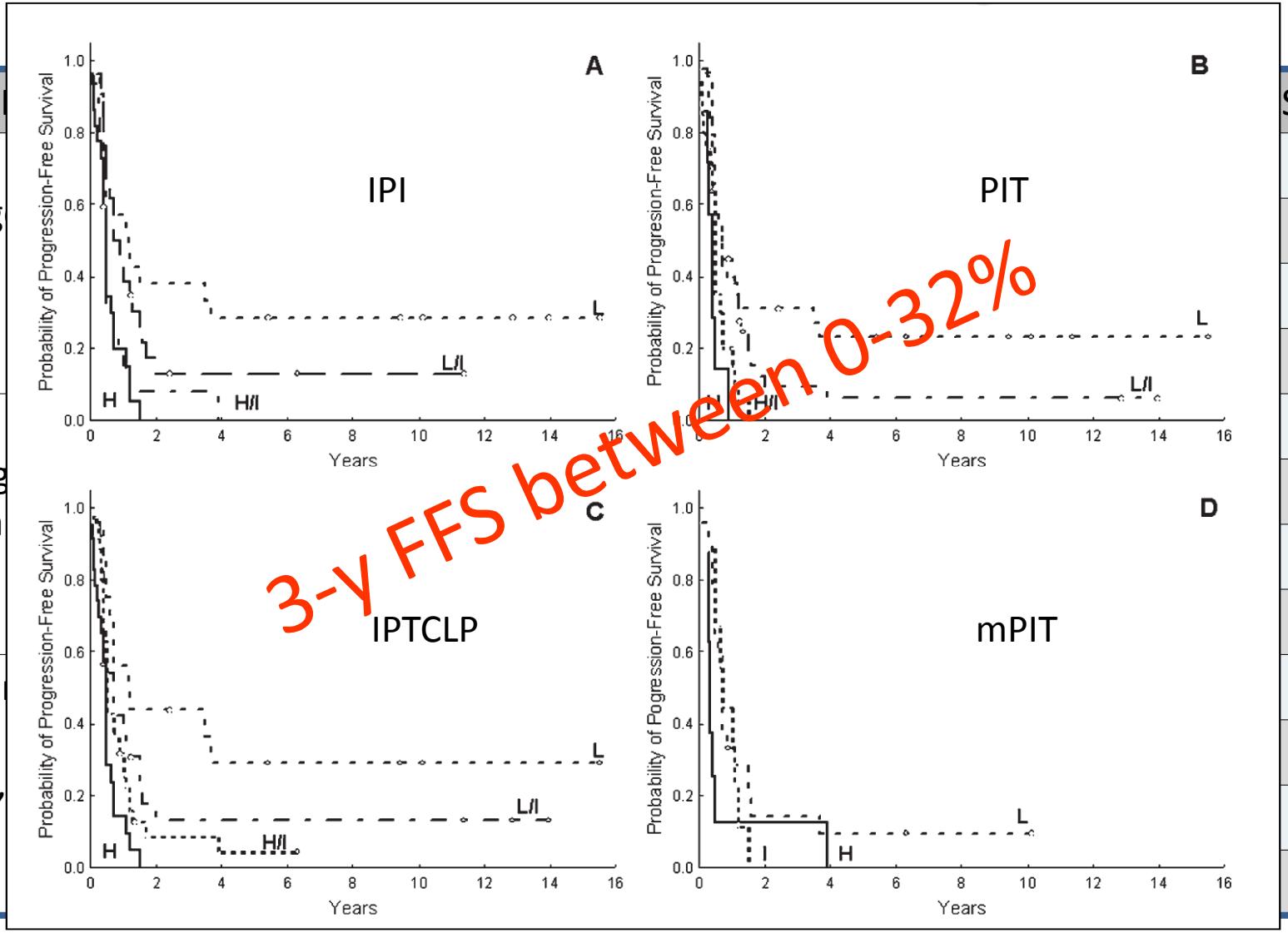
[a]Adapted with permission, The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-hodgkin's lymphoma N Engl J Med 329:987-994, 1993. Copyright © 1993 Massachusetts Medical Society. All rights reserved.

[b]Gallamini A, Stelitano C, Calvi R, et al.: Peripheral T-cell lymphoma unspecified (PTCL-U): A new prognostic model from a retrospective muticentric clinical study. Blood 2004; 103: 2474 - 2479

Horwitz SM: J Natl Compr Canc Netw. 2016 Sep;14(9):1067-79.

PTCL: clinical usefulness of prognostic models

PTCLu + Al					S
IPI	Ag				
PIT	Ag ma				
Internatio	Age,				



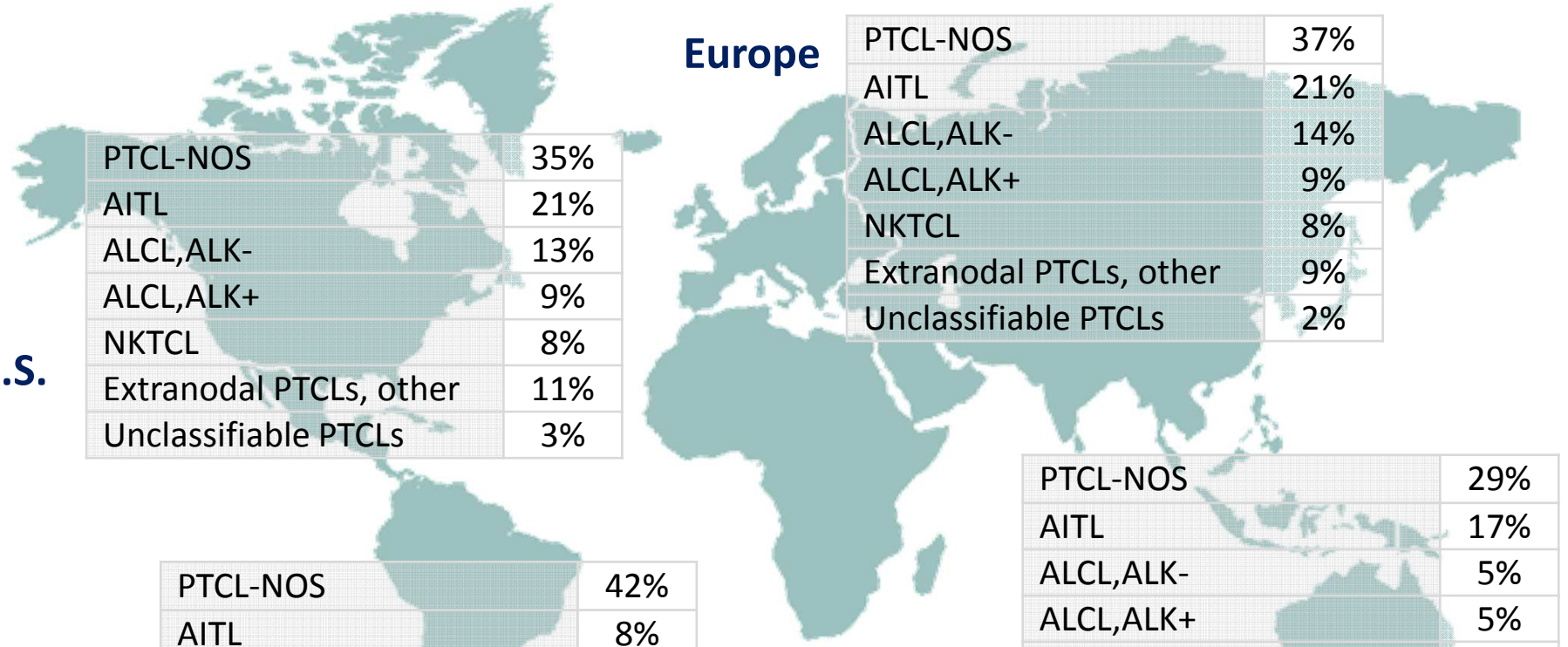
Vose et al. ASH 2005; abstr 811;
Gutierrez-Garcia Ann Oncol 2011; 22, 397-204

IPI, International prognostic index;
FFS, failure-free survival; OS, overall survival

Prospective prognostic models

T-cell Project: subtypes by geographic area

(N=1391 validated on 30/04/2016)



U.S.

PTCL-NOS	35%
AITL	21%
ALCL,ALK-	13%
ALCL,ALK+	9%
NKTCL	8%
Extranodal PTCLs, other	11%
Unclassifiable PTCLs	3%

Europe

PTCL-NOS	37%
AITL	21%
ALCL,ALK-	14%
ALCL,ALK+	9%
NKTCL	8%
Extranodal PTCLs, other	9%
Unclassifiable PTCLs	2%

South America

PTCL-NOS	42%
AITL	8%
ALCL,ALK-	26%
ALCL,ALK+	8%
NKTCL	10%
Extranodal PTCLs, other	4%
Unclassifiable PTCLs	2%

Asia

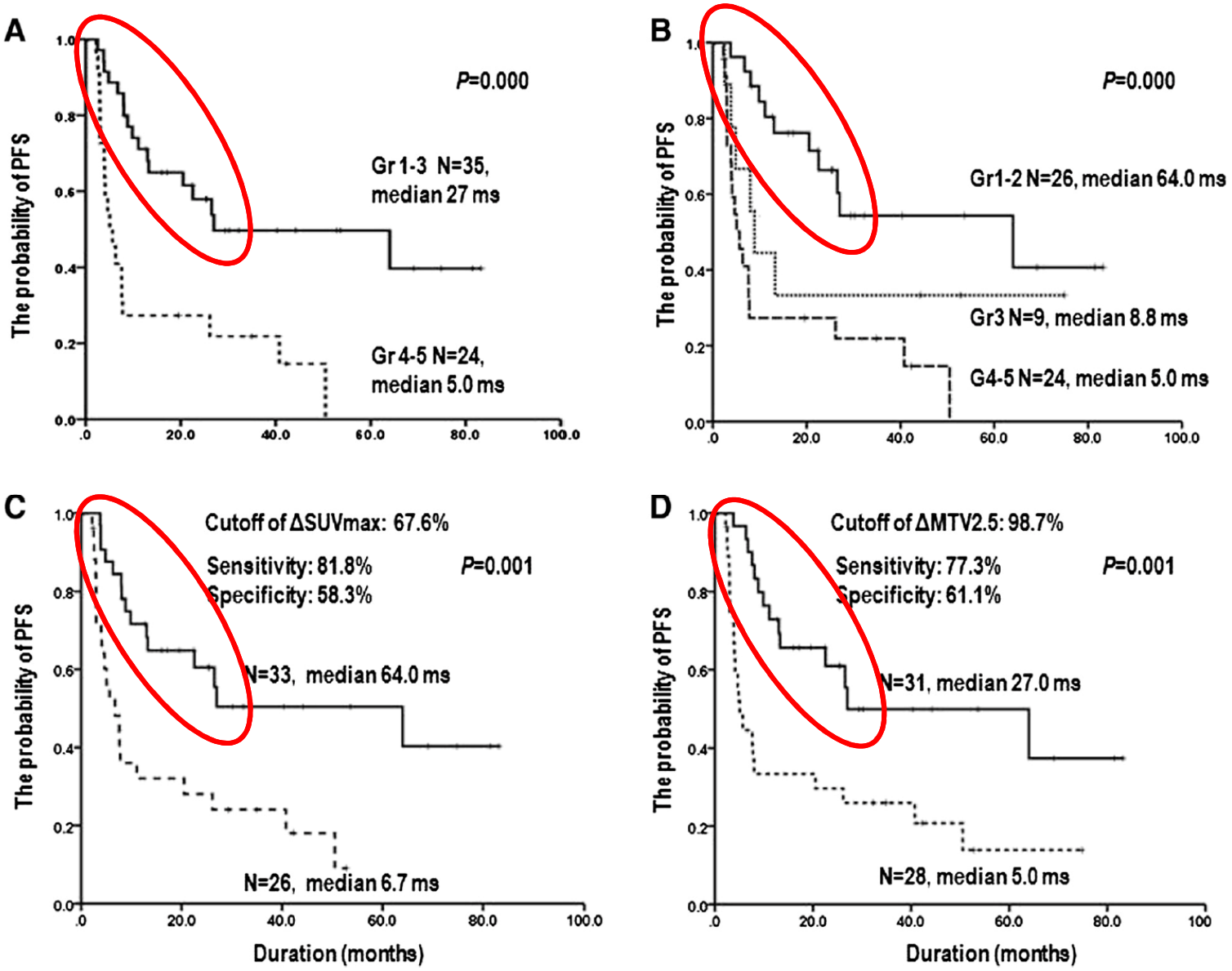
PTCL-NOS	29%
AITL	17%
ALCL,ALK-	5%
ALCL,ALK+	5%
NKTCL	29%
Extranodal PTCLs, other	9%
Unclassifiable PTCLs	6%

Courtesy of M. Federico, September 2016

The role of functional imaging in PTCL

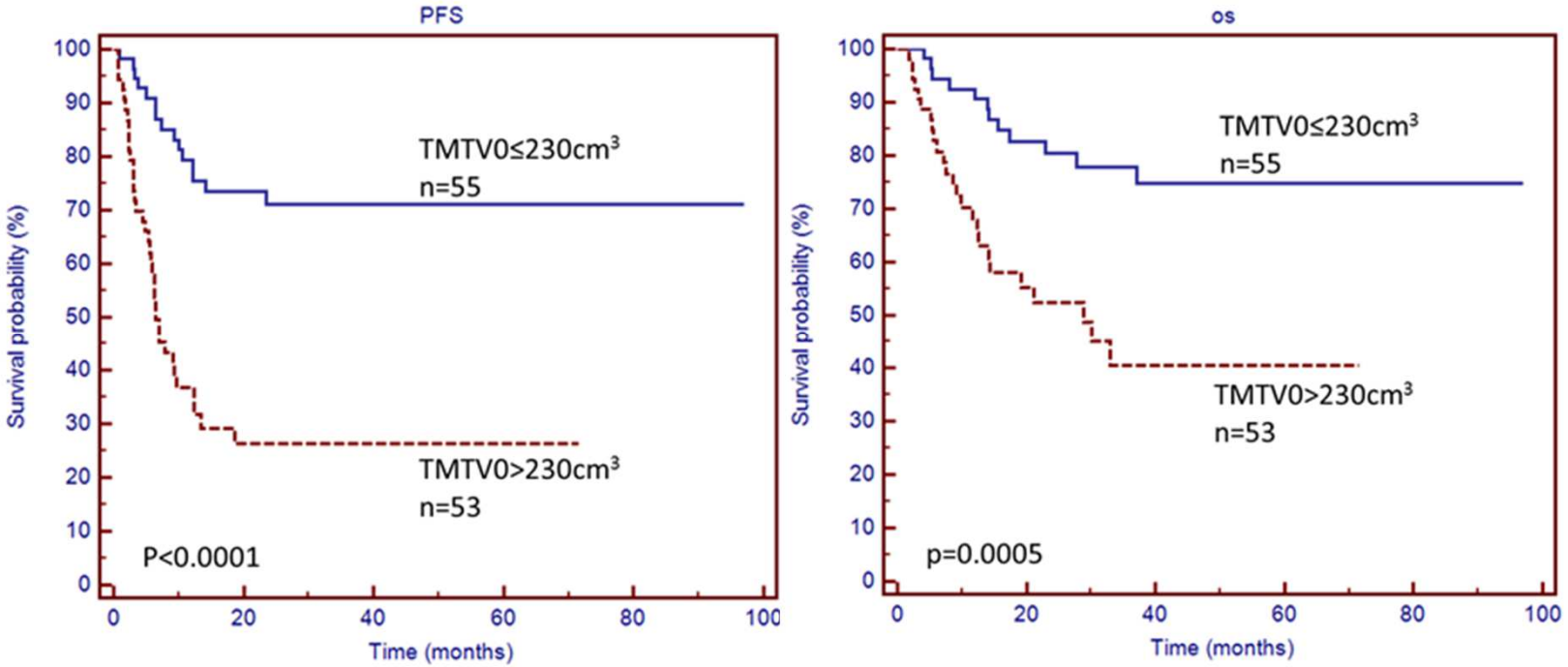
	Prognostic factors	Predictive factors
PROS	Available at baseline for all patients	Include both known and unknown factors
	Allow comparison between groups	Accurate
CONS	Unspecific	Available only during treatment
	Retrospectively arisen	Treatment-restricted

Interim PET in PTCL (N=63)



Jung SH BMC Cancer 2015; 15: 198-210.

Outcome according to MTV



- Median TMTV0 = 224 cm^3 (5-3824 cm^3)
- Cut off 230 cm^3 by ROC analysis

2-year PFS :

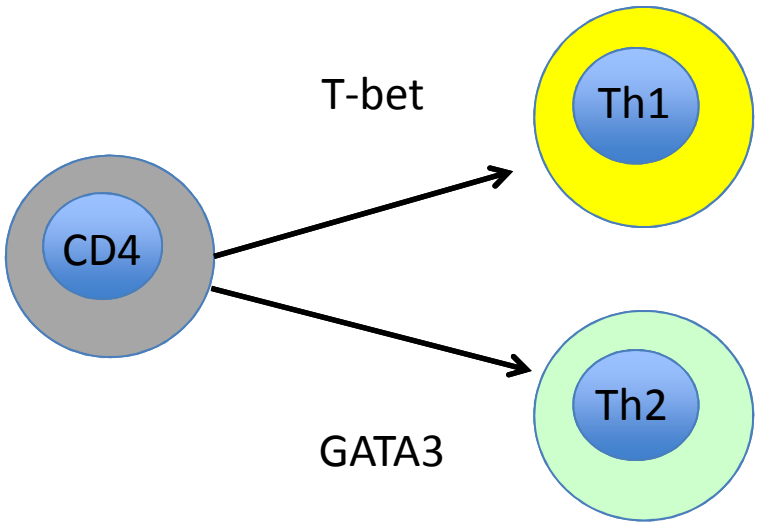
TMTV0 ≤ 230cm^3 : 71% (65-77%)
TMTV0 > 230cm^3 : 26% (20-32%)

2-year OS :

TMTV0 ≤ 230cm^3 : 80% (75-85%)
TMTV0 > 230cm^3 : 50% (42-58%)

Cottereau AS: Haematol. Oncol. 2015; 33 [abstr. 084].

The relevance of master gene expression GATA3 and T-bet responsible for T-cell ontogeny



Broere F: in Nijkamp and Parnham eds. Principles of immunopharmacology. 3rd ed. Springer 2011

LETTERS TO THE EDITOR

C-MYC is related to GATA3 expression and associated with poor prognosis in nodal peripheral T-cell lymphomas

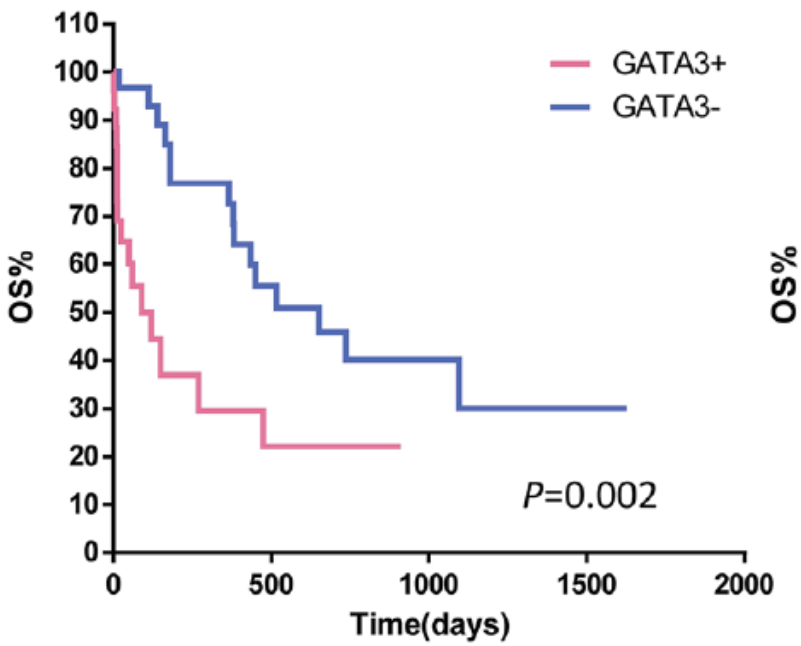
	n-PTCL			PTCL-NOS		
	C-MYC			C-MYC		
C-MYC	–	Ki-67	–	–	Ki-67	–
Ki-67	<0.001	–	GATA3	0.001	–	GATA3
GATA3	0.010	0.754	–	0.004	0.111	–

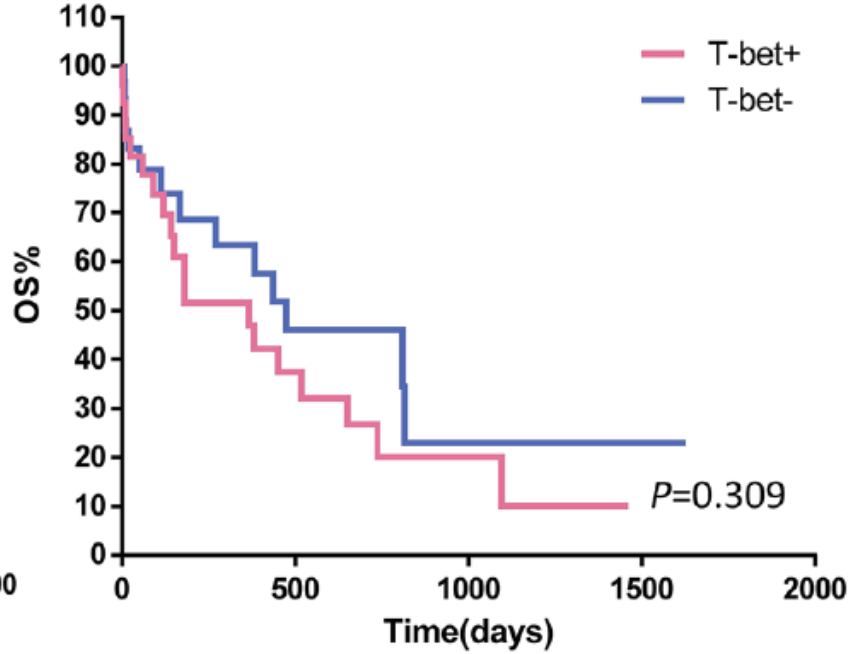
www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2016

GATA3 expression correlates with poor prognosis and tumor-associated macrophage infiltration in peripheral T cell lymphoma

Manso R.: Haematologica. 2016 Aug;101(8):e336-8.
Zhang W: Oncotarget. 2016 Aug 29. doi: 10.18632/oncotarget.11673

GATA3, t-bet and OS in PTCL





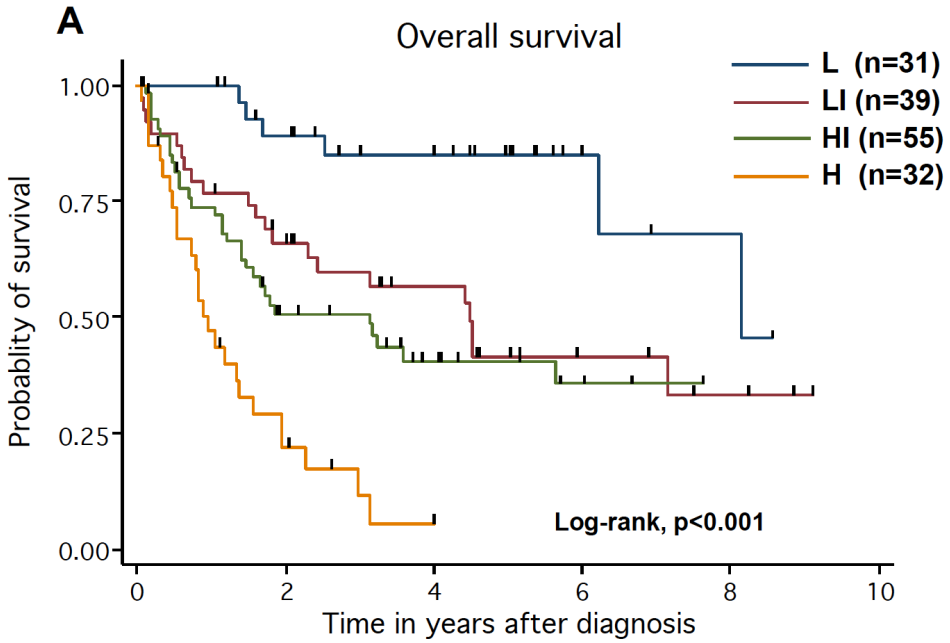
Variable	Univariate survival analysis	Multivariate survival analysis
Age (> 60)	0.353	
Gender (male)	0.337	
B symptom (present)	0.007**	0.801
LDH (elevated)	0.026*	0.100
ECOG (2–4)	0.000**	0.000**
Stage (III–IV)	0.300	
BM involvement (present)	0.063	
IPI score (3–5)	0.001**	0.329
Ki-67 (> 70%)	0.954	
GATA3 (positive)	0.000**	0.004**

Zhang W: Oncotarget. 2016 Aug 29. doi: 10.18632/oncotarget.11673

Angioimmunoblastic T-cell lymphoma (AILT): clinical and molecular prognosticators

Angioimmunoblastic T-cell lymphoma (AILT)

- Median age of patients > 60 years
- Male predominance
- The primary site of disease are the lymph nodes,
- 80%-90% of patients exhibit advanced and ENS disease
- Polyclonal hyper γ-globulinemia, hemolytic anemia, with positive Coombs test
- Proliferation of T^{FH} cells with a CD10+, CXCL-13+, PD-1+ and EBER-ISH+ phenotype.



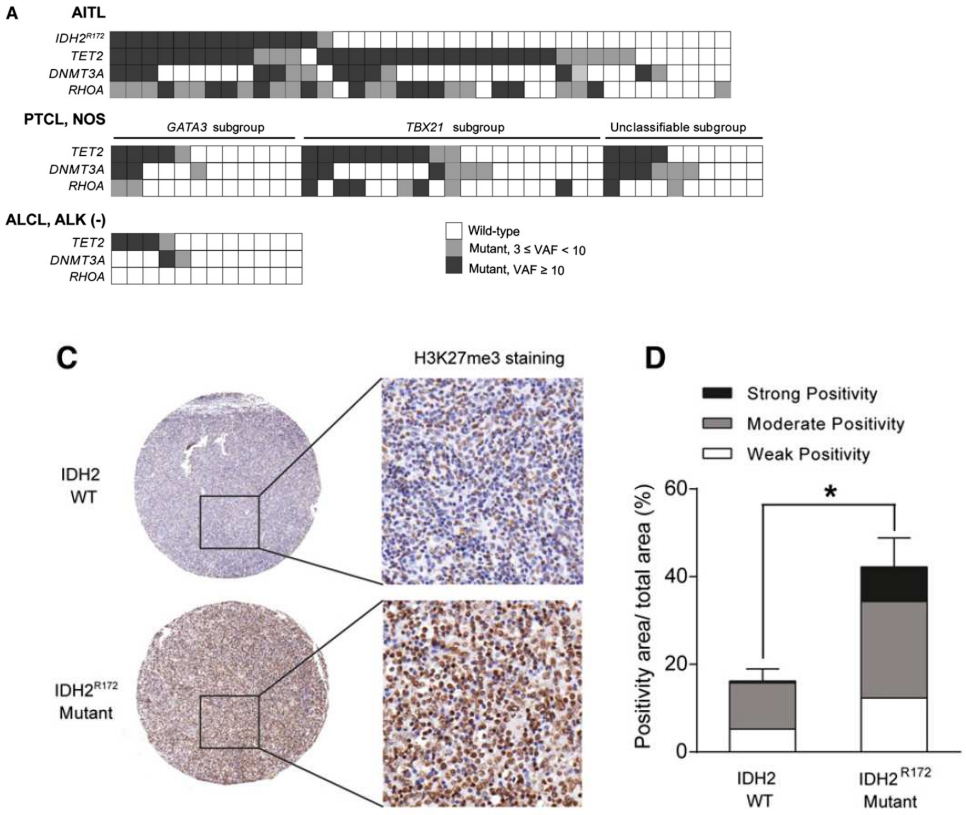
PROGNOSTIC FACTORS

- Age > 60
- WBC >10.000/µl
- Elevated IgA (>400 mg/dl)
- Hb <13 (M), < 11 (F) gr/dl
- Platelets < 150.000/µl
- ENS > 1

Group 1: 0-1 factors; group 2: 2 factors; group 3: 3 factors; group 4: 4-6 factors.

Tokunaga M: Blood. 2012;119(12): 2837-2843

IDH2^{R172}/TET2 are specific epigenetic mutations in AILT



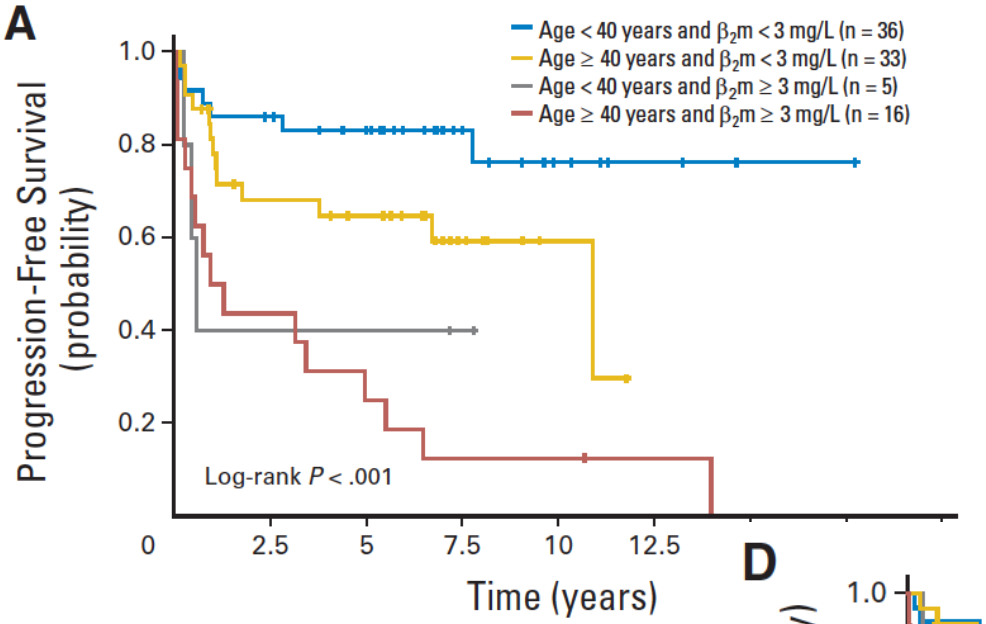
- IDH2 ^{R172} : Epigenetic alteration with aberrant DNA and histone metylation.
- Found in 32.8% of AILT cases and only 1/24 PTCL-NOS
- IDH2^{R172}/TET2 mutation enriches the T^{FH} phenotype.
- Mutant IDH2 inhibits various histone demethylases.
- In AITL significantly elevated levels of H3K27me3 (metylated histone) are found.

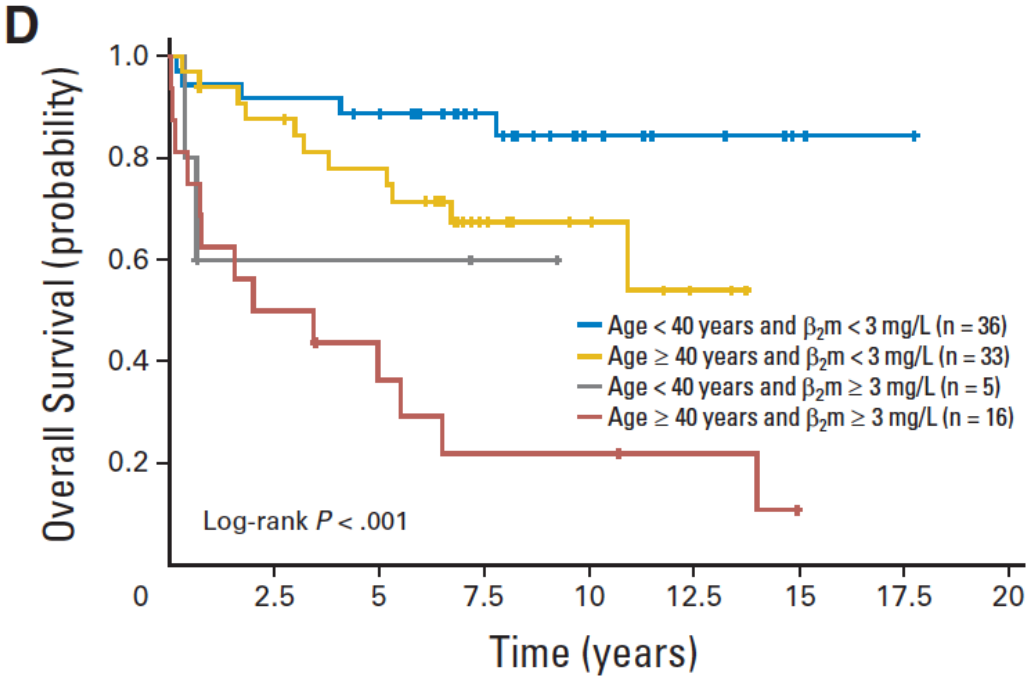
Wang C. Blood. 2015;126(15):1741-1752

Anaplastic Large-cell Lymphoma (ALCL): clinical, immunohistochemical and molecular prognosticators

138 adult ALCL patients
46% Alk+, 54% Alk-
On behalf of GELA/LYSA

Age and $\beta_2$microglobulin in ALCL



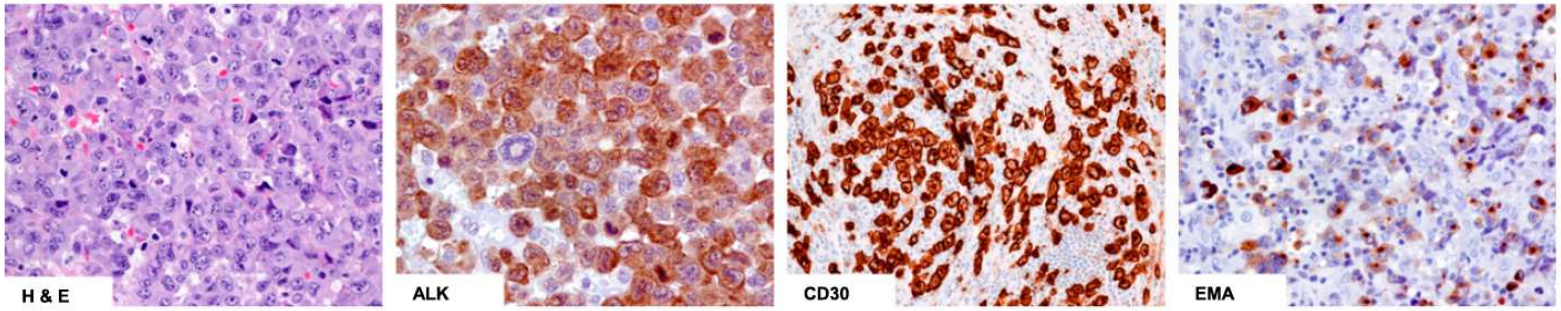


β_2-microglobulin > 3 mg/L
Age > 40 years.

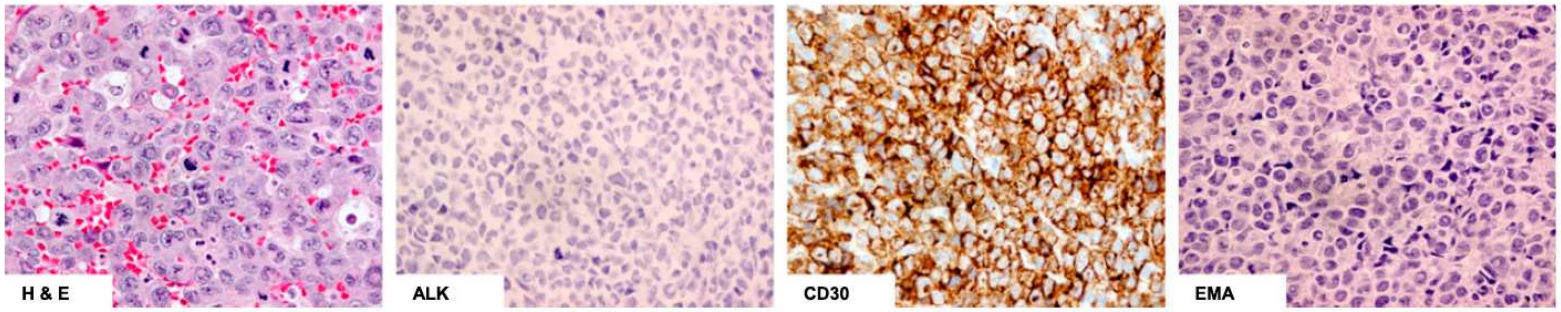
Sibon D: J Clin Oncol 2012; 30:3939-3946.

Anaplastic Large-Cell Lymphoma (ALCL)

ALCL ALK+



ALCL ALK-

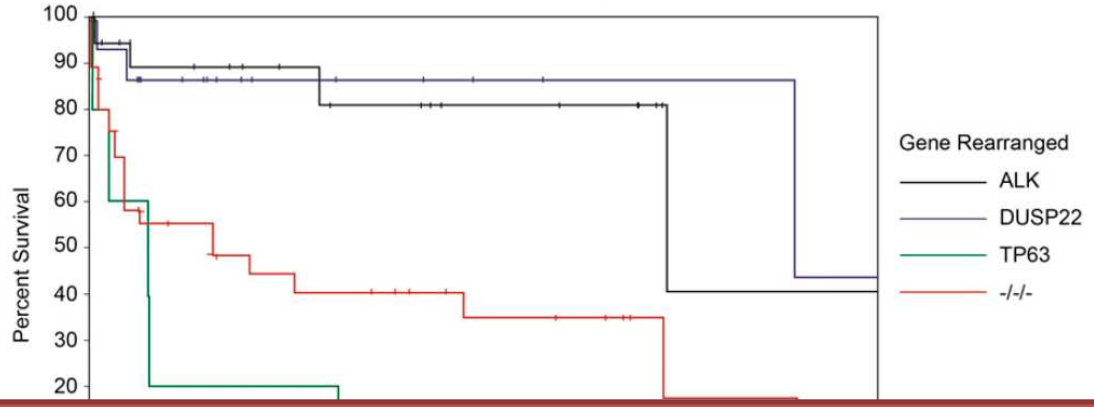


ALCL Alk+: CD 30+, Alk+, EMA +
ALCL Alk-: CD 30+, Alk-, EMA -

5-year FFS, 36% versus 20%, respectively; p=0.012
5-year OS, 49% versus 32%, respectively; p=0.032

Hapgood G: Blood. 2015;126(1):17-25

ALCL : Immunohistochemistry, cytogenetics and molecular profile



In the future, combining clinical and genetic biomarkers may aid in risk stratification and help guide initial patient management.

Recurrent translocations involving ALK	Recurrent translocations involving *DUSP22:IRF4*
t(2;5)(p23;25) *ALK:NPM1* (85%)	(6p25.3) (30%)
t(2;v) (15%)	Recurrent translocations involving *TP63* (3q28) 8%
Gains: 7, 17p, 17q	Gains: 1q, 6p, 8q, 12q
Deletions: 4, 11q, 13q	Deletions: 6q, 4q, 13q

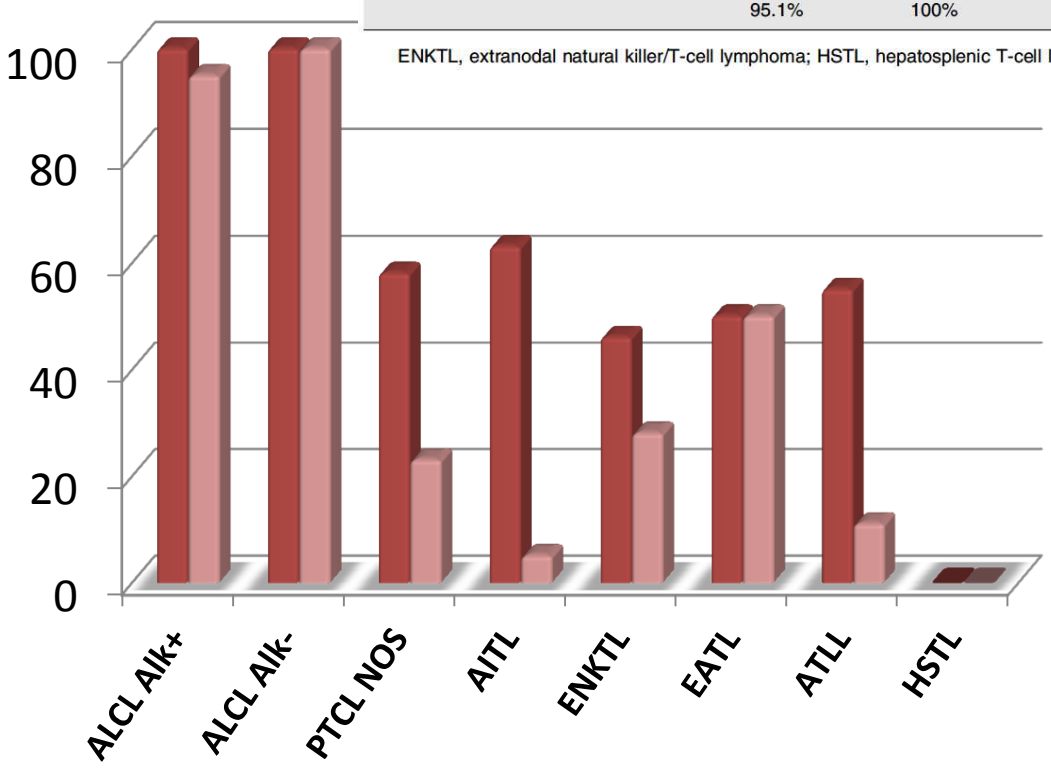
Hapgood G: Blood. 2015;126(1):17-25

CD 30 expression in peripheral T-cell lymphoma

CD 30 expression in PTCL

% of CD30$^+$ tumor cells	ALCL ALK$^+$ (N = 61)	ALCL ALK$^-$ (N = 19)	PTCL NOS (N = 141)	AITL (N = 97)	ENKTL (N = 28)	EATL (N = 14)	ATLL (N = 9)	HSTL (N = 7)
Score 0	0	0	59	36	15	7	4	7
<5%			42%	37%	53.5%	50%	44%	100%
Score 1	0	0	37	46	2	0	1	0
5-24%			26%	47%	7%		11%	
Score 2	3	0	13	10	3	0	3	0
25-49%	5%		9%	10%	11%		33%	
Score 3	1	0	14	5	4	1	1	0
50-75%	2%		10%	5%	14%	7%	11%	
Score 4	57	19	18	0	4	6	0	0
>75%	93%	100%	13%		14%	43%		
Total positive cases (scores 1-4)	61	19	82	61	13	7	5	0
	100%	100%	58%	63%	46%	50%	55.5%	
Strongly positive cases (scores 3-4)	58	19	32	5	8	7	1	0
	95.1%	100%	23%	5%	28.5%	50%	11%	

ENKTL, extranodal natural killer/T-cell lymphoma; HSTL, hepatosplenic T-cell lymphoma.

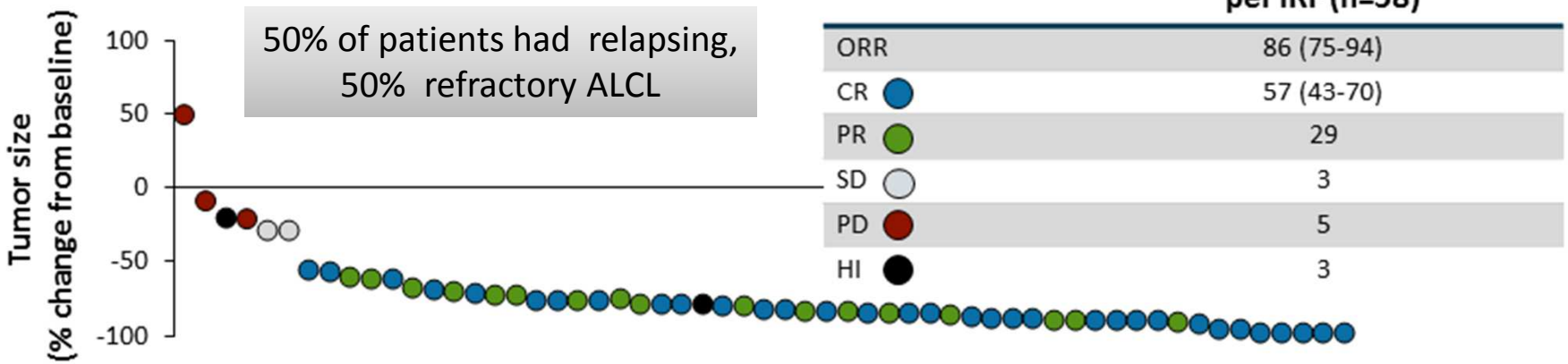


Positive (5-75%)

Strongly pos.(> 50%)

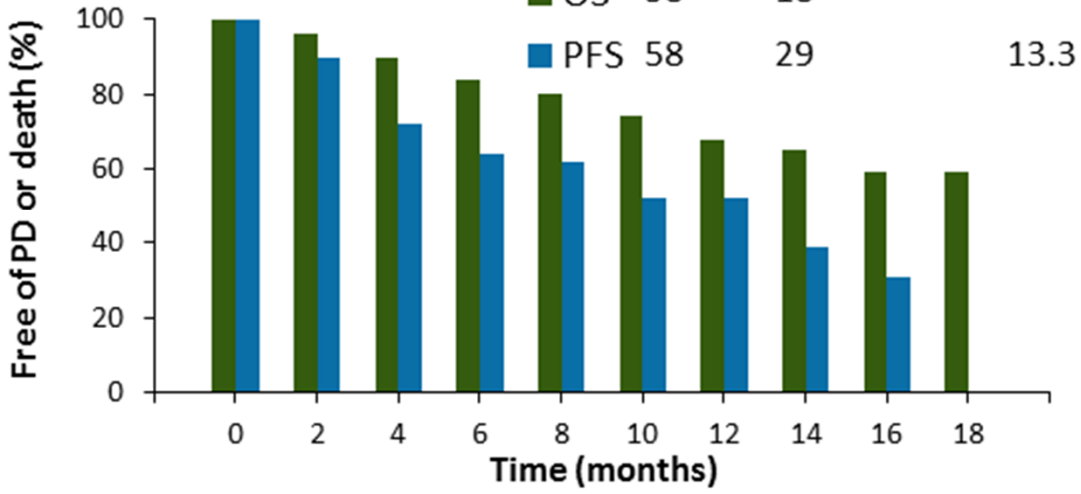
Bossard C.: Blood. 2014;124(19):2983-2986

Brentuximab Vedotin Effective in Patients With R/R ALCL



Response, % (95% CI) per IRF (n=58)	
ORR	86 (75-94)
CR	57 (43-70)
PR	29
SD	3
PD	5
HI	3

- Reduction in tumor volume was observed in 97% of patients



	n	Events	Median (months)
OS	58	18	-
PFS	58	29	13.3

- Median OS was not reached at the time of the analysis; 18 patients had died
- Median PFS among all patients was 13.3 months by IRF

Pro B, et al. *J Clin Oncol.* 2012;30(18):2190-2196.

Brentuximab Vedotin Sequentially With CHOP or Combined With CHP in Front-line CD30+ PTCL

Disease diagnoses included:

- 32 patients with systemic ALCL
  - ALK-positive, n=6
  - ALK-negative, n=26
- 7 patients with other CD30+ PTCL
  - PTCL-NOS, n=2
  - AITL, n=2
  - Enteropathy-associated T-cell lymphoma, n=1
  - Adult T-cell leukemia/lymphoma, n=2

Best response after sequential or combination treatment

	Sequential		Combination			
	ALCL (n=13)		ALCL (n=19)		Non-ALCL (n=7)	
Response	**n**	**%**	**n**	**%**	**n**	**%**
ORR	11	85	19	100	7	100
CR	8	62	16	84	7	100
PR	3	23	3	16	0	
SD	0		0		0	
PD	2	15	0		0	

Response assessment at cycle 8 (sequential treatment), cycle 6 (combination treatment), or at last available response assessment for patients who discontinued treatment before these time points.

Fanale MA, et al. *J Clin Oncol.* 2014;32(28):3137-3143.

Conclusions

- PTCL are an heterogeneous group of diseases with a very dismal prognosis
- Central pathology review to reference pathology lab is mandatory, as the reproducibility of diagnosis is only 70% in expert hands.
- Prognostic models are only able to predict a poor or a very poor treatment outcome.
- PET imaging + traditional prognostic markers should be assessed in prospective trials.
- CD 30 is highly expressed in several PTCL subsets and anti CD 30 mo Abs proved very active both in relapse and first-line treatment of PTCL

Thank you for the attention

Pr. Andrea Gallamini

Research, Innovation and Statistics.

A. Lacassagne Cancer Center, Nice - France

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